

Proposed Plan and Rationale to Support a SA4Ag Indication in Elective Orthopedic Surgery

**Vaccines and Related Biological Products
Advisory Committee**

November 7, 2017



Proposed Plan and Rationale to Support a SA4Ag Indication in Elective Orthopedic Surgery

William Gruber, MD, FAAP, FIDSA

SVP Vaccine Clinical Research and Development
Pfizer Inc.

November 7, 2017

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Presentation Overview

Topic	Presenter
Spinal Surgery and Infection	Thomas Errico, MD Professor of Orthopedic Surgery and Neurosurgery Chief, Division of Spine Surgery NYU School of Medicine NYU Langone Orthopedic Hospital
Orthopedic Infections: Challenging Problem	Javad Parvizi, MD, FRCS James Edwards Professor of Orthopedic Surgery Sidney Kimmel School of Medicine Rothman Institute at Thomas Jefferson University
Proposed Plan and Rationale to Support a SA4Ag Indication in Elective Orthopedic Surgery	William Gruber, MD, FAAP, FIDSA Senior Vice President Vaccine Clinical Research and Development Pfizer Inc.

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Additional Experts in Sponsor Section

Expert	Area of Expertise
William J. Richardson, MD Professor of Orthopedic Surgery, Division Chief of Adult Spine Surgery Director of the Professional Accountability Program Duke University Health System	Orthopedic Surgeon, Spine Surgeon
Mark E. Shirtliff, PhD Professor, Department of Microbial Pathogenesis School of Dentistry and School of Medicine University of Maryland	<i>Staphylococcus aureus</i> Biofilms



Department of Orthopedic Surgery

Spinal Surgery and Infection

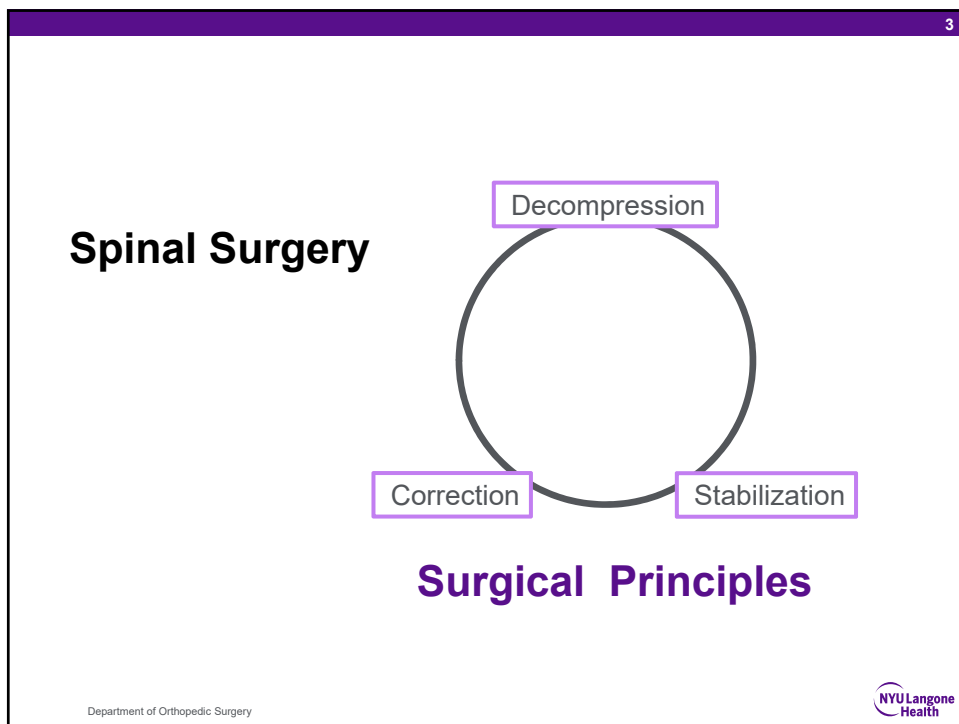
Thomas J. Errico, MD

Professor of Orthopedic Surgery and Neurosurgery
Chief, Division of Spine Surgery
NYU School of Medicine
NYU Langone Medical Center
NYU Langone Orthopedic Hospital



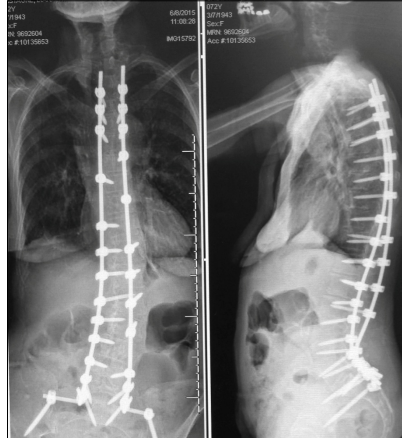
Disclosures

1. Fastenetix: Royalties
2. K2M: Speaking and/or Teaching Arrangements; Trips/Travel
3. Pfizer: Research Support (Investigator Salary, Staff/Materials)
4. OMEGA: Fellowship Support paid to the institution
5. Spine Research: Grants/Research Support



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Post Operatively



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Clinical History

- 63 year old female status post 5 back operations in Florida by the same surgeon
- 1st operation L4/5 instrumented laminated fusion for Degenerative Spondylolisthesis
- Needed 4 more operations each left her standing more crooked
- Advised by her surgeon to seek psychiatric counseling
- Unable to stand straight
- Less than one block ambulation because of thigh pain and weakness bilaterally

Pre-op X-rays



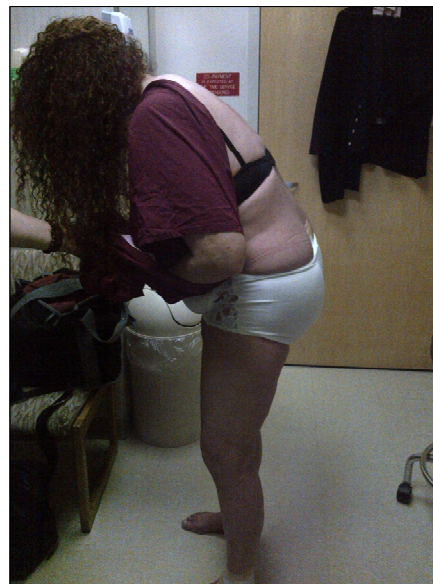
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Pre-op Clinical View

Note stooped over posture

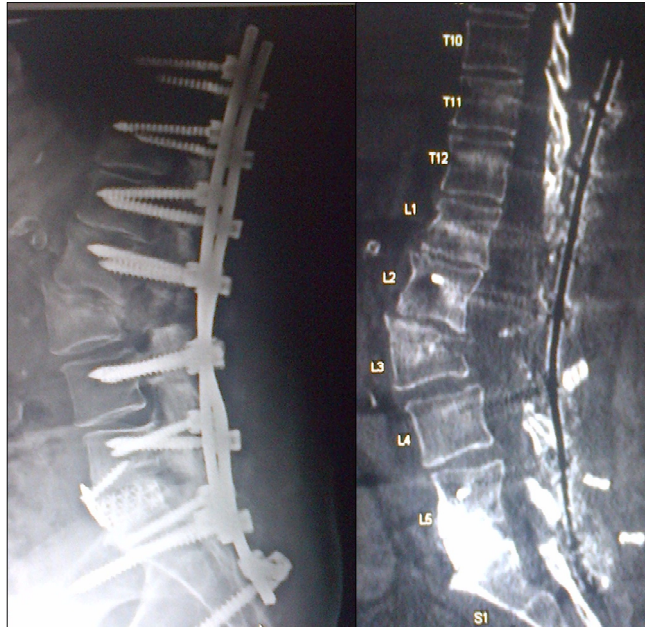
Inability to look ahead



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Operation



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Pre and Post Op Clinical



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Step-by-Step Treatment of an Acute Deep Wound Infection Following Long Segment Spinal Fusion for Adult Kyphoscoliosis

Case presentation of Spinal Deformity created by *Staph aureus* Infection

Infection After Spinal Surgery

- Spinal surgery SSIs incidence is 1.9% (median 3.3%, range 0.1%–22.6%)¹
 - Pooled average contribution of *S. aureus* to spinal SSIs is 49.3% (median, 50.0%; range, 16.7%–100%)¹
 - Instrumented spinal fusion has the highest SSI incidence¹
- Direct healthcare costs are nearly twice as high for patients who develop spinal surgery SSIs compared to non-SSI-infected patients¹
- Despite efforts to reduce SSI incidence, *S. aureus* SSIs still complicate spinal surgery putting patients at risk for related morbidity and mortality




1. Patel H, et al. Surg Infect (Larchmt) 2017;18(4):461-73.
Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5466015/>

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Case

- 70 y.o. female
- PMH - diabetes, atrial fibrillation, congestive heart failure
- Chronic debilitating pain
- **Multiple back surgeries complicated by *Staph aureus* infection**
- Pseudoarthrosis and Progressive pitching forward
- Can't stand erect
- **Bony destruction at L4-5 due to osteomyelitis (MRSA) for which she took antibiotics for 6 months**




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Operative Treatment

- T10-Pelvis posterior spinal fusion with multiple osteotomies
- Anterior lumbar interbody fusion (ALIF) L5-S1
- L4-5 partial corpectomies with bone grafting



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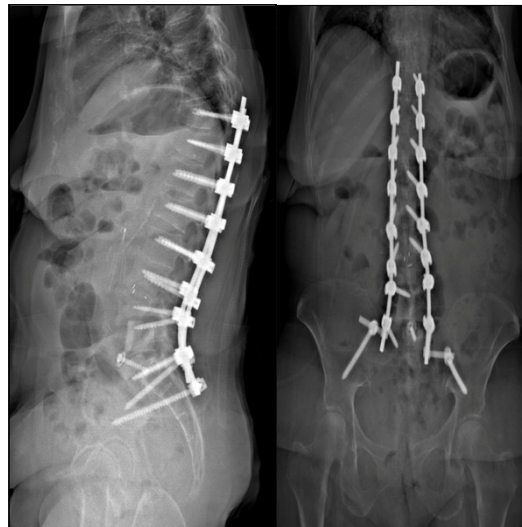
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3 weeks Post-op

- Persistent drainage from bottom of the incision
- No fevers/ constitutional symptoms
- Leg pain and back pain improved
- Labs:
 - Erythrocyte Sedimentation Rate (ESR) – 105
 - White Blood Count (WBC) - Elevated
 - **Culture from wound drainage - *Staph aureus***
- Radiology:
 - Hardware intact
- Treatment:
 - Antibiotics started according to results of Sensitivity
 - Planned for re-exploration

Surgical Exploration


- Infected Seroma at right Iliac fixation site debrided and drained
- Intra-operative cultures sent
- No loosening of hardware noted
- Repeat right-sided gluteal flap closure by Plastic Surgeon
- Antibiotics } 9 weeks



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3 Month Follow-up

- **At 3 months follow up**
 - Patient weaned off antibiotics
 - Progressive rehabilitation with independence in walking and activities of daily living
- **Physical Exam**
 - **Midline posterior spinal incision healed with 2 small pinhole openings at the inferior most aspect draining blood tinged drainage. No collection or induration**
- **Radiology**
 - Proximal Junctional Kyphosis (PJK)
 - Hardware intact
- **Labs**
 - ESR- 93, WBC - Elevated
 - Culture - positive for *Staph aureus*




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Debridement and Re-exploration

- Right Iliac side hardware prominent
- No evidence of infection deep to fascia
- Thorough debridement done
- Right sided Iliac screw side-connector cut short
- Right gluteal myofascial re-advancement flap
 - Post-op care
 - Drains in place for 2 weeks
 - Antibiotics through PICC line



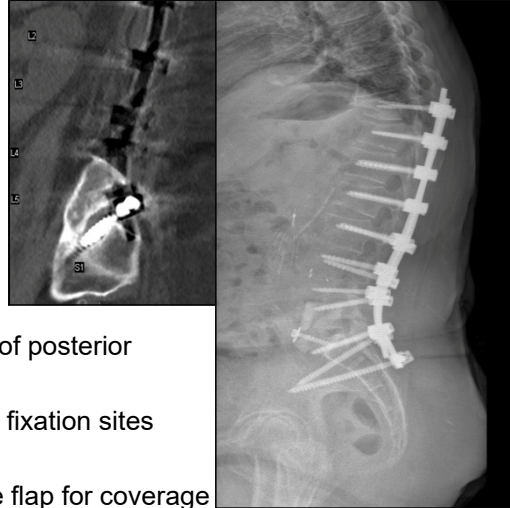
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At 1 Year Follow-up

- Persistent drainage
- New onset lumbosacral pain
- Radiology
 - Bilateral Iliac **screw loosening** **Stable wedge compression fracture at T11**
- Re-exploration and removal of posterior hardware
- Purulent discharge from iliac fixation sites on pressing in midline
- 640cm of para-spinal muscle flap for coverage



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Post-op care

- Cultures were again positive for *S. aureus*
- 12 week of antibiotics
- 3 drains kept in for 3 weeks
- No evidence of wound dehiscence
- Progressive increase in back pain
- Plan
 - Revision posterior instrumentation from T4-Pelvis due to increase in back pain

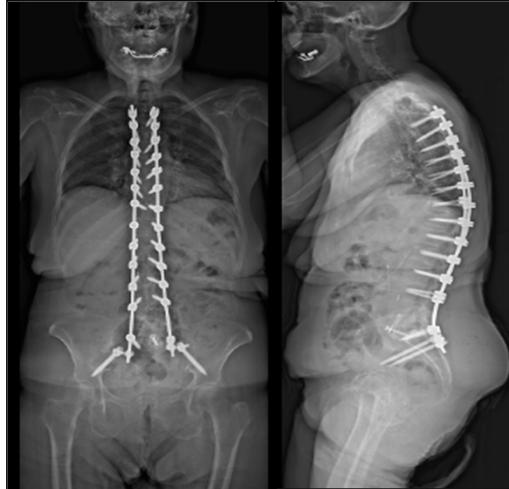


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Final Follow-up

- 3 Months IV Antibiotics
- Life Long Oral Suppressive Meds
- Life Long Risk of Recurrence
- Multiple Hospitalizations
- Long Term Care Facility
- Medical Costs
 - NYU Hospital Charges: **\$2 million**
 - NYU Hospital Reimbursement: **\$400,000**





Challenges to Enrollment in STRIVE Study

- 21 subjects enrolled to date
- Enrollment started Sept 2015
- 2400 adult and pediatric spine surgeries per year
 - Approx. 10% undergoing STRIVE index procedure
- Despite initial enthusiasm – barriers to enrollment
 - Patients do not like to enroll in studies
 - Added burden of additional visits and blood draws
 - Overwhelmed by condition and planned surgical procedure
- Pharma study run by surgeons used to medical device trials




Thank You





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INSTITUTE




Thomas
Jefferson
University


Orthopedic Infections Challenging Problem

Javad Parvizi MD, FRCS
James Edwards Professor of Orthopedics
Rothman Institute at Thomas Jefferson
University, Philadelphia

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Conflict of Interest




■ I am a paid consultant to Pfizer

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True Genius Today

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- Themistokles Gluck
- 1890: first ivory knee replacement

.... ailments of human will be treated by artificial materials...

THEMISTOKLES GLUCK



Th. Gluck

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Total Joints in US


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- 620,000 Total Knee Arthroplasties
- 310,000 Total Hip Arthroplasties

27,000 revisions for PJI in 2013

Maltenfort et al MSIS 2012 4

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Total Joints in US

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- Over **1,000,000** in 2013
Health Statistics 2014
- Over **3,500,000** TKA by year 2030
Cram P et al. *JAMA* 2012

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Periprosthetic Joint Infection (PJI)

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- 1979s – Sir John Charnley

...joint sepsis will be the major hurdle in our way in the future...



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■ EDITORIAL

Periprosthetic joint infection

THE LAST FRONTIER

J. Parvizi,
F. S. Haddad


*From The British
Editorial Society of
Bone and Joint
Surgery, London,
United Kingdom*

The number of publications in the literature related to periprosthetic joint infection (PJI) has risen 100 fold during the last decade. This confirms the fact that this is a dreaded complication in the minds of the medical community. Infection also strikes fear in the hearts of patients who contemplate joint replacement, arguably one of the most successful surgical procedures. The challenges that PJI pose are many. Despite intense interest over the years, we could argue that little has changed in the


sophisticated, sensitive and specific tests. It is likely that they will ultimately be used at the bedside.⁴

John Herzenberg and his group⁵ highlight a series of complex infections that are seen with external fixators, including necrotising fasciitis and toxic shock syndrome, both of which must be recognised early by orthopaedic surgeons, and both of which require early intervention. Strategies to avoid such severe complications would clearly be welcome.⁶

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Periprosthetic Joint Infection



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- Incidence 1-4% of primary lower limb arthroplasties



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Periprosthetic Joint Infection




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- May occur in >30% after revision arthroplasty



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Periprosthetic Joint Infection




■ Majority (>50%) are caused by *Staph aureus*

Aggarwal, VK et al. *J Knee Surg* 2014 11



The True PJI Incidence Rates is Underestimated in the Registries



Acta Orthopaedica 2009; 79(12): 405-412

Low rate of infected knee replacements in a nationwide series—is it an underestimate?

Review of the Finnish Arthroplasty Register on 38,676 operations performed 1997 through 2003

Esa Järvenpää^{1,2}, Kaisa Huotari³, Heini Huhtala⁴, Juha Nevalainen⁵, and Yrjö T. Konttinen⁶

¹Medical school, University of Tampere, Tampere; ²Centra Hospital for Joint Replacement, Tampere; ³Division of Medicine, Helsinki University Central Hospital, Helsinki; ⁴Tampere School of Public Health, University of Tampere; ⁵Department of Orthopedics, University of Kuopio, Kuopio; ⁶Department of Medicine, Helsinki University Central Hospital, Helsinki

J Hosp Infect. 2010 Jul;75(3):205-9. doi: 10.1016/j.jhin.2009.10.029. Epub 2010 Mar 12.

Disease burden of prosthetic joint infections after hip and knee joint replacement in Finland during 1999-2004: capture-recapture estimation.

Huotari K¹, Lytikäinen O, Oksanen J, Vartiainen MJ, Seitsalo S, Pajunen R, Rantanen P. Hospital Infection Surveillance Team.

Author information

¹Helsinki University Central Hospital, PO 348, 00029 HUS, Finland. kaisa.huotari@hus.fi

Acta Orthop Scand. 2004 Aug;75(4):434-41.

Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications.

Pedersen A¹, Johnsen S, Overgaard S, Seiballe K, Sørensen HT, Lucht U.

Author information

¹Department of Orthopaedics, Aarhus University Hospital, Denmark. abp@soci.au.dk

J Arthroplasty. 2000 Oct;15(7):884-9.

Are the findings in the Swedish National Total Hip Arthroplasty Register valid? A comparison between the Swedish National Total Hip Arthroplasty Register, the National Discharge Register, and the National Death Register.

Söderman P¹, Malchau H, Herberts P, Johnell O

Acta Orthop. 2006 Feb;77(1):49-56.

Registration completeness in the Norwegian Arthroplasty Register.

Espehaug B¹, Furnes O, Havelin LI, Engesaeter LB, Vollset SE, Kindseth O

Acta Orthop. 2015 Jun; 86(3): 277-278.


Published online 2015 May 13. doi: [10.3109/17453674.2015.1042320](https://doi.org/10.3109/17453674.2015.1042320)

PMCID: PMC4443466


The rate of prosthetic joint infection is underestimated in the arthroplasty registers

Eivind Witso[✉]

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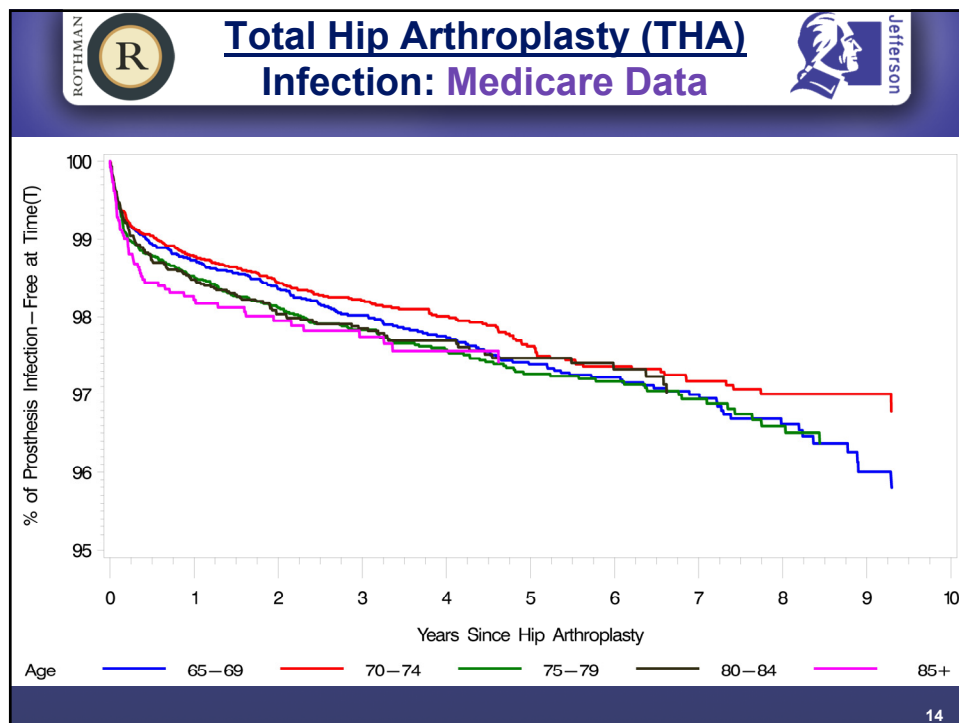
Periprosthetic Joint Infection (PJI)
Conclusions

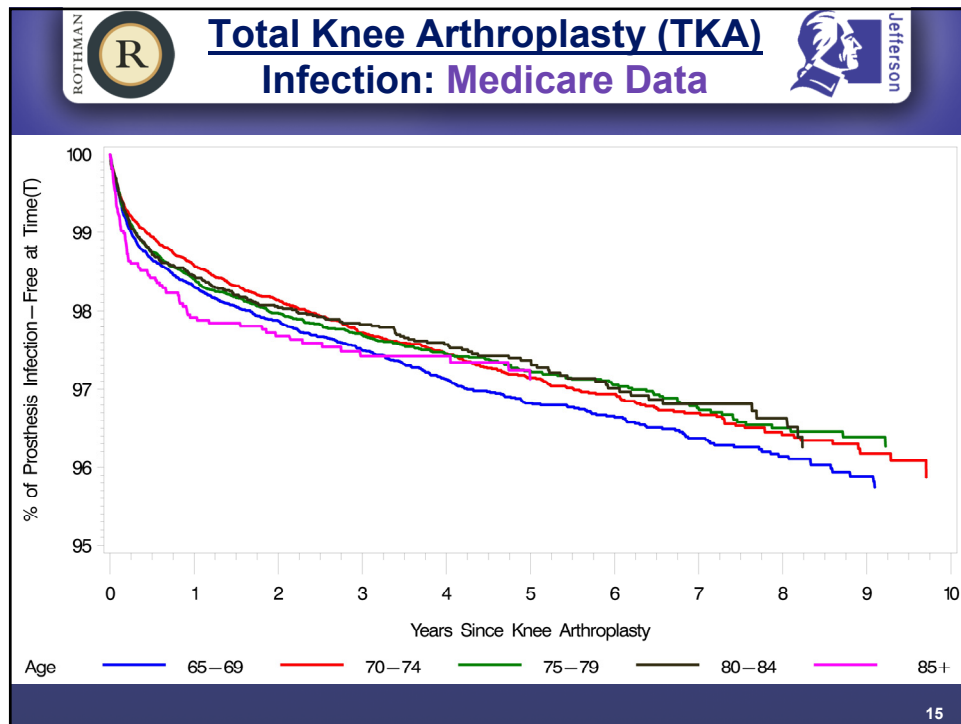


- Incidence and prevalence is higher than believed
- 12% of so called “aseptic” could have PJI

Parvizi J , et al *CORR* 2011

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Periprosthetic Joint Infection (PJI)

- Over 75% of infections occur within 90 days of surgery

Kurtz SM et al. *J Arthroplasty* 2012

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Economic Burden of Periprosthetic Joint Infection in the United States

Steven M. Kurtz, PhD,*† Edmund Lau, MS,‡ Heather Watson, PhD,‡
Jordana K. Schmier, MA,§ and Javad Parvizi, MD

Abstract: This study characterizes the patient and clinical factors influencing the economic burden of periprosthetic joint infection (PJI) in the United States. The 2001-2009 Nationwide Inpatient Sample was used to identify total hip and knee arthroplasties using *International Classification of Diseases, Ninth Revision*, procedure codes. The relative incidence of PJI ranged between 2.0% and 2.4% of total hip arthroplasties and total knee arthroplasties and increased over time. The mean cost to treat hip PJIs was \$5965 greater than the mean cost for knee PJIs. The annual cost of infected revisions to US hospitals increased from \$320 million to \$566 million during the study period and **was projected to exceed \$1.62 billion by 2020.** As the demand for joint arthroplasty is expected to increase substantially over the coming decade, so too will the economic burden of prosthetic infections. **Keywords:** periprosthetic joint infection, total knee arthroplasty, total hip arthroplasty.
© 2012 Published by Elsevier Inc.



Background



Increasing knowledge
has led to many
official diagnostic recommendations

IDSA



MSIS




AAOS





ICM






Prevention of Surgical Site Infection





World Health Organization




World Health Organization


Patient Safety

A World Alliance for Safer Health Care


WHO Guidelines for Safe Surgery 2009

Safe Surgery Saves Lives 

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Periprosthetic Joint Infection





Clinical Review & Education

JAMA Surgery | Special Communication

Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017

Sandra I. Bertoni-Torres, MD; Craig A. Umscheid, MD, MSc; Dale W. Bruckner, DO, MPH; Brian Lewis, MA, MD; Erin C. Stone, MA; Rachel S. Mills, MSc; Caroline E. Reinde, MD, MSPH; Sherry Morgan, RN, MSL, PhD; Joseph D. Saloner, MD; John E. Meunier, MD, PhD; E. Patricia Dellinger, MD; Karol M. F. Lam, MD; Kim F. Berbari, MD; John Segreti, MD; Javed Parvizi, MD; Juan Blazquez, MD, PhD, RN, CNOR, CIC; George Allen, PhD, CIC, CNOR; Jan A. J. W. Kluytmans, MD; Rodney Dorian, PhD; William P. Schector, MD, for the Healthcare Infection Control Practices Advisory Committee

IMPORTANCE: The human and financial costs of treating surgical site infections (SSIs) are increasing. The number of surgical procedures performed in the United States continues to rise, and surgical patients are initially seen with increasingly complex comorbidities. It is estimated that approximately half of SSIs are deemed preventable using evidence-based strategies.

OBJECTIVE: To provide new and updated evidence-based recommendations for the prevention of SSI.

EVIDENCE REVIEW: A targeted systematic review of the literature was conducted in MEDLINE, EMBASE, CINAHL, and the Cochrane Library from 1968 through April 2014. A modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence and the strength of the resulting recommendation and to provide explicit links between them. Of 5487 potentially relevant studies identified in literature searches, 1702 titles and abstracts were screened, and 1696 underwent full-text review by 2 independent reviewers. After exclusions, 170 studies were extracted into evidence, evaluated, and categorized.

FINDINGS: Before surgery, patients should shower or bathe (full body) with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before the operative day. Antimicrobial prophylaxis should be administered only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made. In cesarean section procedures, antimicrobial prophylaxis should be administered before skin incision. Skin preparation in the operating room should be performed using an alcohol-based agent unless contraindicated. For clean and clean-contaminated procedures, additional prophylactic antimicrobial agent doses should not be administered after the surgical incision is closed in the operating room, even in the presence of a drain. Topical antimicrobial agents should not be applied to the surgical incision. During surgery, glycemic control should be implemented using blood glucose target levels less than 200 mg/dL, and normothermia should be maintained in all patients. Increased fraction of inspired oxygen should be administered during surgery and after extubation in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation. Transfusion of blood products should not be withheld from surgical patients as a means to prevent SSI.


Invited Commentary

Supplemental content


Author Affiliations: Author affiliations are listed at the end of this article.

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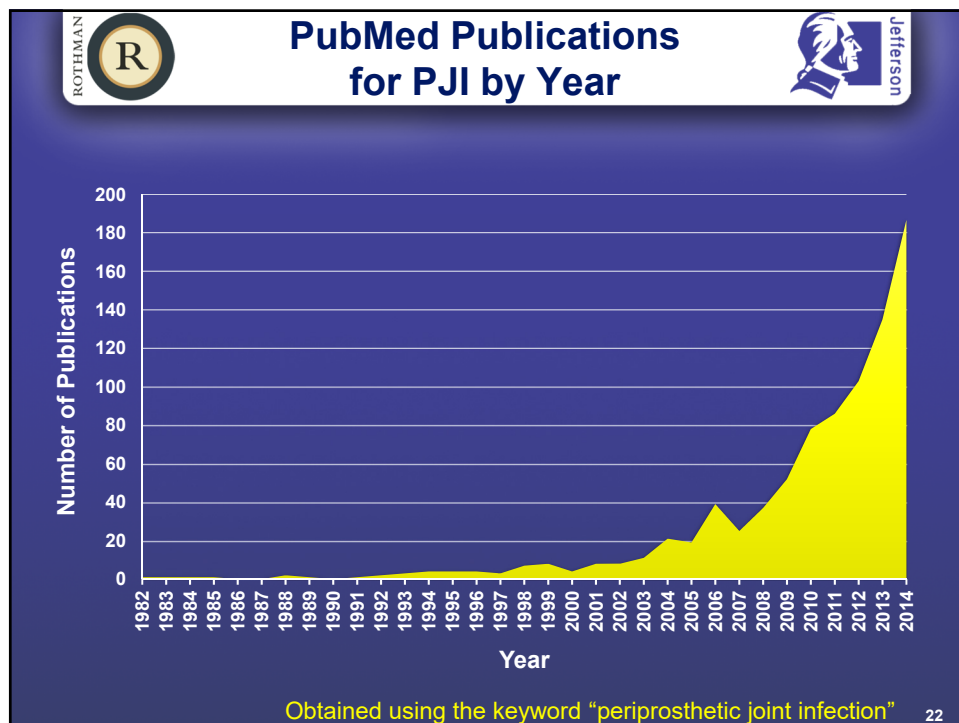
Periprosthetic Joint Infection (PJI)
Challenges

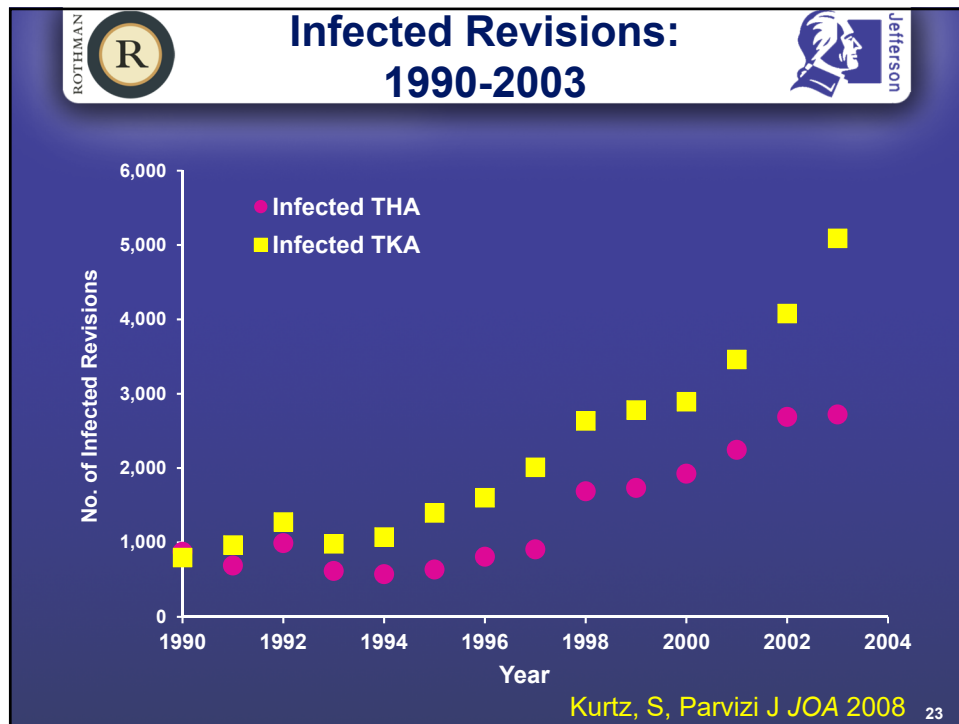


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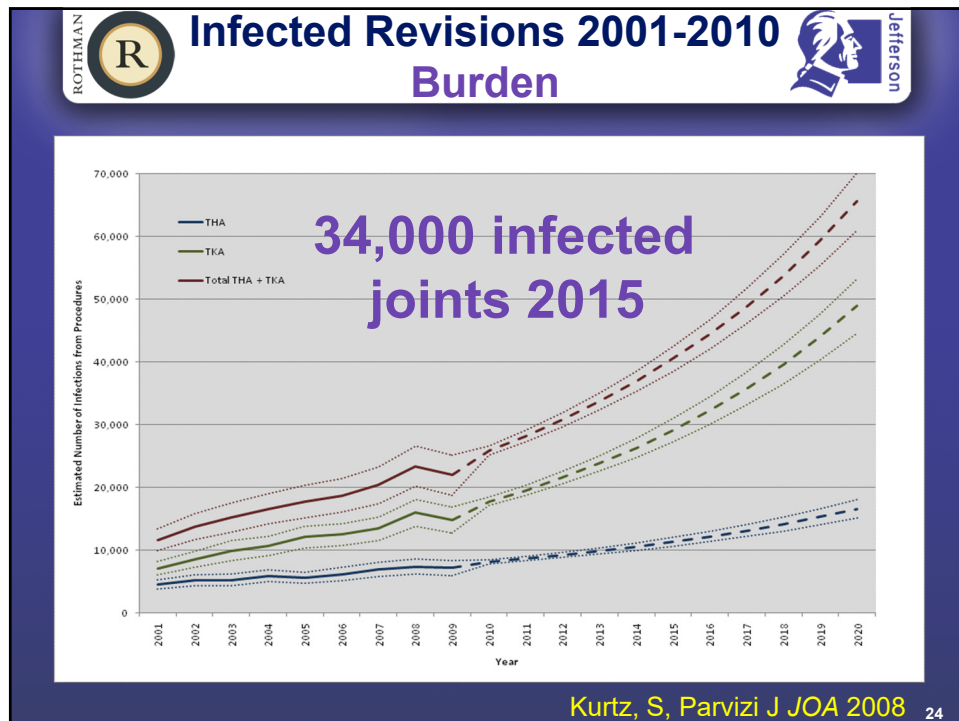
All infections are on the rise

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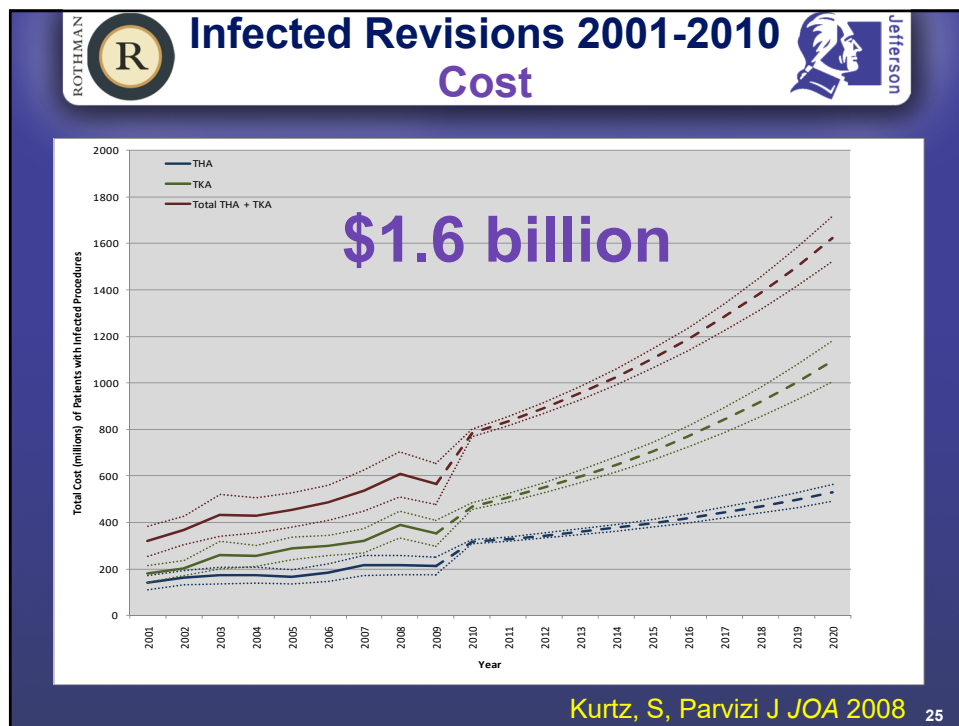






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ROTHMAN  **Cost of Treating Periprosthetic Joint Infection (PJI)** 

■ ???? ?

J Arthroplasty, 2010 Sep;25(6 Suppl):103-7. doi: 10.1016/j.arth.2010.04.011. Epub 2010 May 31.

Periprosthetic joint infection: the economic impact of methicillin-resistant infections.

Parvizi J¹, Pawasarat IM, Azzam KA, Joshi A, Hansen EN, Bozic KJ.

⊕ **Author information**

Abstract

The orthopedic community has begun to witness a worrisome rise in the incidence of periprosthetic joint infections (PJIs) caused by resistant organisms. Besides other challenges associated with treating these infections, it appears that these infections may pose a higher cost compared to infections caused by sensitive organisms. Significantly higher cost of care for treatment of infections due to methicillin-resistant organisms were seen at a mean of \$107,264 per case compared to \$68,053 for treating PJI caused by sensitive strains ($P < .0001$). More effective strategies for preventing the spread of infections caused by resistant organisms need to be implemented to ease the social and economic strains facing the orthopedic community due to resistant organisms.

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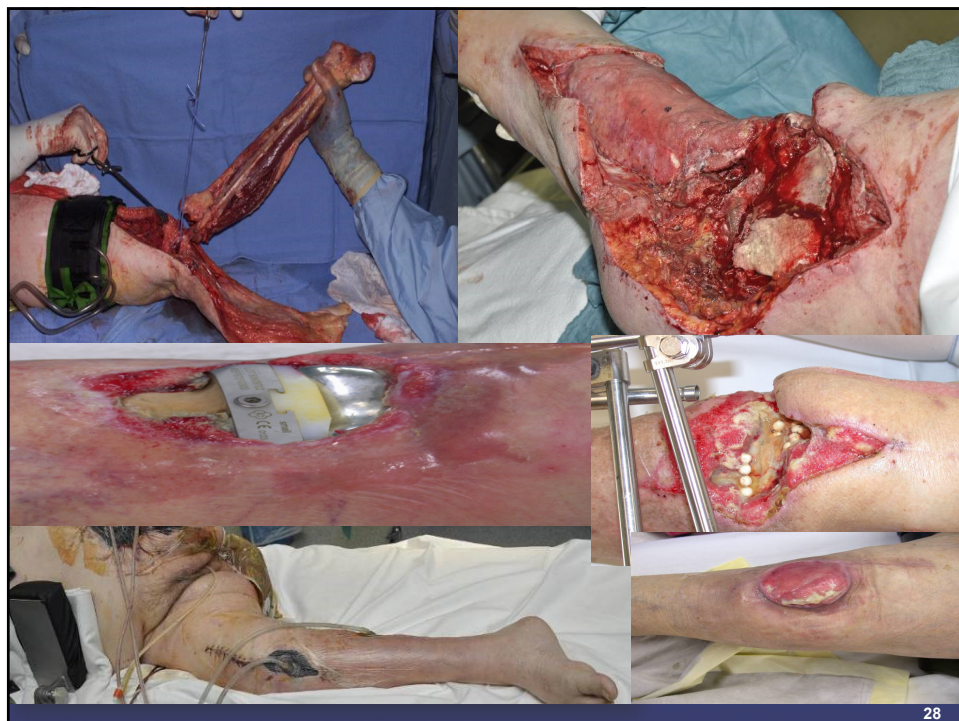
Periprosthetic Joint Infection (PJI)
Challenges

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High morbidity



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Periprosthetic Joint Infection (PJI) Challenges

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Infection kills



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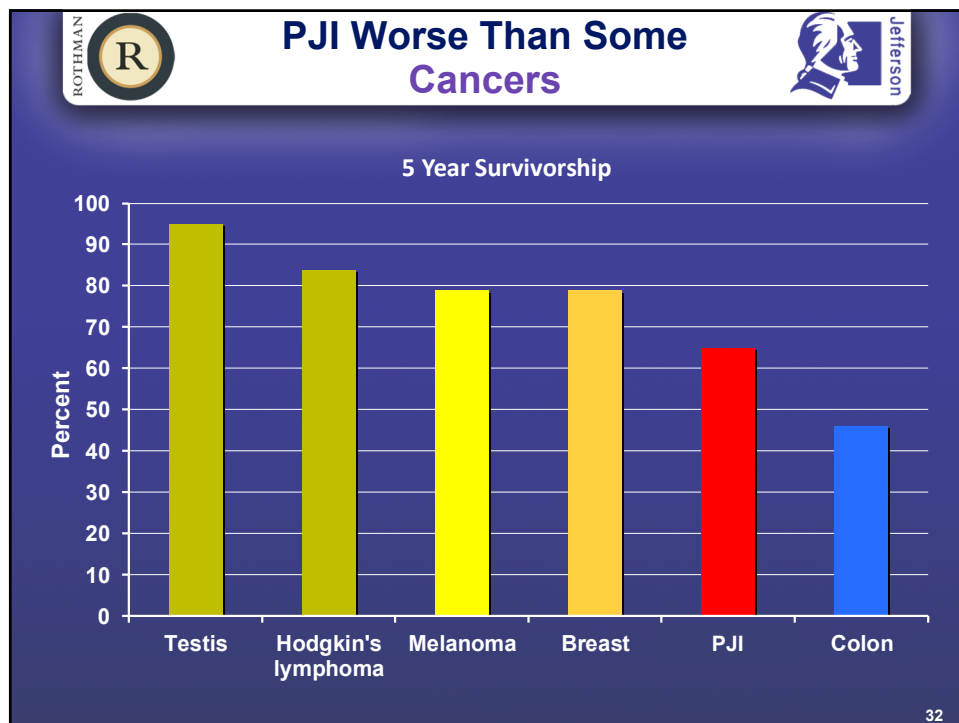




Rothman Study




- PJI is an independent predictor of mortality
 - When adjusting for confounders, PJI is associated with a **4x** increased odds of one-year mortality compared to aseptic revision

Zmistowski B et al JBJS 2013 31






Mortality after TJA Medicare Study





Are We Winning or Losing the War with PJI: Trends in PJI and Mortality Risk for the Medicare Population

Steven M. Kurtz PhD
Edmund Lau MS
Min-Sun Son PhD
Ellen T. Chang ScD
Werner Zimmerli MD
Javad Parvizi MD





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Research Question

- We asked:
 1. Is the incidence of PJI changing over time?
 2. Is mortality risk after PJI changing over time?

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Methods

Study Cohort

- Study Cohort
 - Medicare Inpatient Claims Data (2005-2015)
 - 100% inpatient data
 - Patients (65+)
- Primary TKA patients: 2,527,579 patients
- TKA patients with PJI undergoing surgery: 34,144 patients
- Mortality identified using the companion “denominator file” issued with the data set

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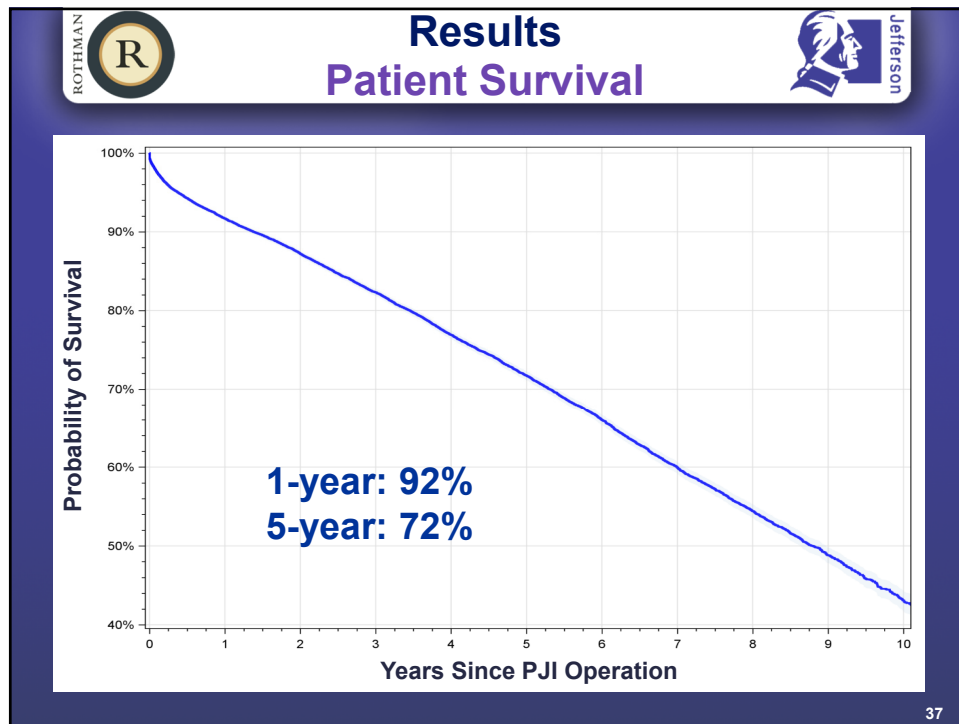


Methods

Statistical Model


- Multivariate Cox proportional hazards regression model
- Mortality and PJI treatment modeled as competing risks
- Adjusted for numerous patient and clinical factors

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- Summary of Findings**
- 5-year overall survival of PJI patients is comparable to two of the most common cancers
 - TKA: 72%
 - Breast cancer: 73%
 - Prostate cancer: 79%
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Future




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- Future needs to be different
- Need for truly novel approach
- Non-antibiotic approach

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AMR: A Crisis



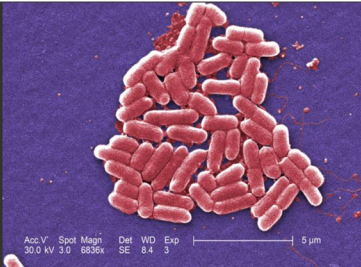
Jefferson

 **REUTERS**

HEALTH


Fri May 27, 2016 | 9:50 PM EDT

U.S. sees first case of bacteria resistant to last-resort antibiotic




The *mcr-1* plasmid-borne colistin resistance gene has been found primarily in *Escherichia coli*, pictured.
REUTERS/COURTESY CDC

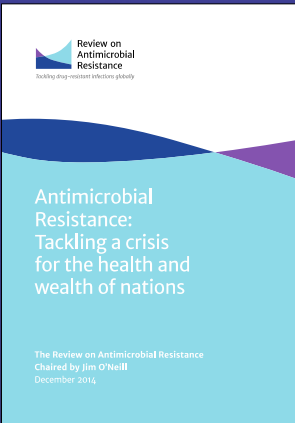
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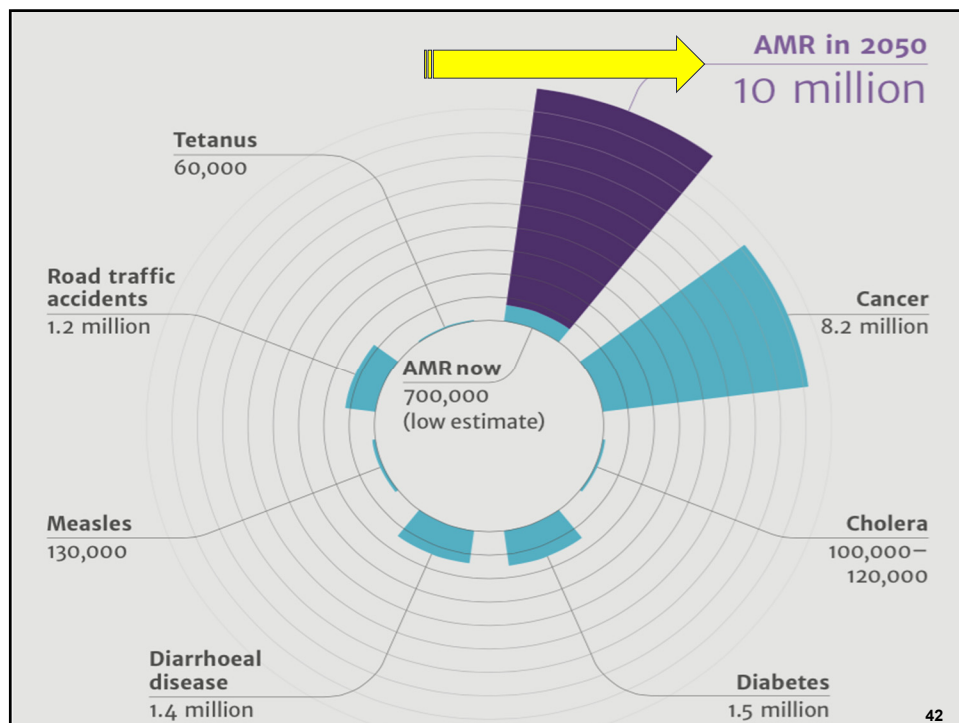
Antimicrobials Issues





- Antimicrobial Resistance (AMR)
- 50,000 deaths/yr (Europe and US)



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Antimicrobials Issues

- Use of antibiotic increased by 40% between 2000 to 2010

Van Boeckel, TP et al. *The Lancet Infectious Diseases* 2014

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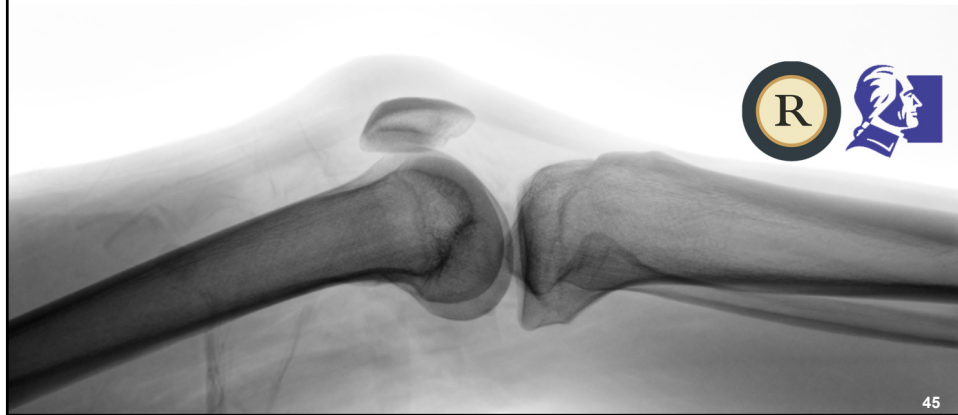


Future

- Enhancing patient immunity to fight infection (cancer)
- Vaccination - exciting and appealing approach
- Staph infections in spine and joints

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THANK YOU



Proposed Plan and Rationale to Support a SA4Ag Indication in Elective Orthopedic Surgery

William Gruber, MD, FAAP, FIDSA

SVP Vaccine Clinical Research and Development
Pfizer Inc.

November 7, 2017

CC-1

Presentation Agenda

**Significant health burden of postoperative
S. aureus infections following elective
orthopedic surgery**

Pfizer's Proposal

**Pathophysiology of postoperative surgical
site infection and rationale for vaccine design**

**STRIVE study design and the justification for
application of safety and efficacy to all adult
elective orthopedic surgery populations**

CC-2

Postoperative Orthopedic *S. aureus* Infections Continue to Be a Serious Public Health Threat

- Most frequently isolated organism in orthopedic surgical site infections (SSIs)¹
- Orthopedic SSIs are associated with increased length of stay (2-3-fold) and mortality (8-12-fold)^{2,3,4}
- Causes nearly half of invasive SSIs in orthopedic surgical populations
 - 41% are methicillin resistant¹
- 9.7 million spinal procedures and 17.8 million arthroplasty procedures are anticipated between 2021-2030 in the United States
- Assuming the current epidemiology, these procedures could lead to:⁵
 - 182,000 *S. aureus* infections
 - 89,000 invasive *S. aureus* infections
 - 140,000 hospitalizations
 - 3,200 deaths

1. Solomkin JS, et al. Surg Infect 2017; 18(4):385-93; 2. Patel, H. et al. Surg Infect 2016; 17(1): 78-88; 3. Poultsides LA et al. J Arthroplasty 2013; 28(3): 385-389; 4. Patel, H. et al. Surg Infect 2017; 18(4): 461-473; 5. Extrapolated from: Life Science Intelligence Report 2015, HCUP 2014, Pfizer Premier Study.

CC-3

Ongoing STRIVE Study *ST*aphylococcus *aureus* suRgical Inpatient Vaccine Efficacy

- Global, placebo-controlled, randomized, double-blind study evaluating the safety, tolerability, and efficacy of SA4Ag in patients undergoing elective, open posterior, multilevel, instrumented spinal fusion procedures in adults aged 18 to 85 years
- Assess efficacy of SA4Ag in the prevention of postoperative *S. aureus* deep incisional or organ/space surgical-site infection and/or bloodstream infection within 90 days
- STRIVE is currently a Phase 2b study with plans to convert to a Phase 3 study with ~90% power to demonstrate vaccine efficacy with a LCI $\geq 20\%$ for SA4Ag assuming a true efficacy of $\geq 70\%$
- ~6000 enrolled subjects planned (~3000 vaccine, ~3000 placebo)

CC-4

Pfizer Proposal

- **Assume** the STRIVE study demonstrates SA4Ag acceptable safety and efficacy in adults
- **Then** STRIVE results should be representative of safety and efficacy in elective orthopedic surgical populations 18 years of age and older

CC-5

Proposed Indication and Dose

“Active immunization for the prevention of postoperative invasive disease caused by *Staphylococcus aureus* in adults 18 years of age and older undergoing elective orthopedic surgery”

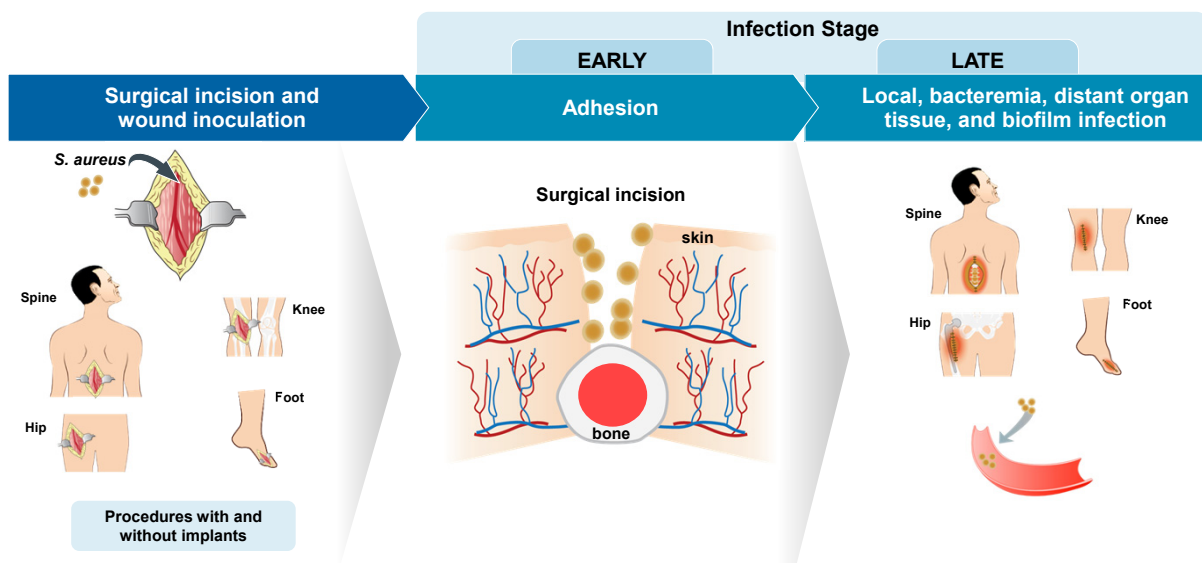
**Single 0.5 mL IM administration
10-60 days prior to surgery**

CC-6

Pathophysiology of Postoperative Surgical Site Infection and Rationale for Vaccine Design

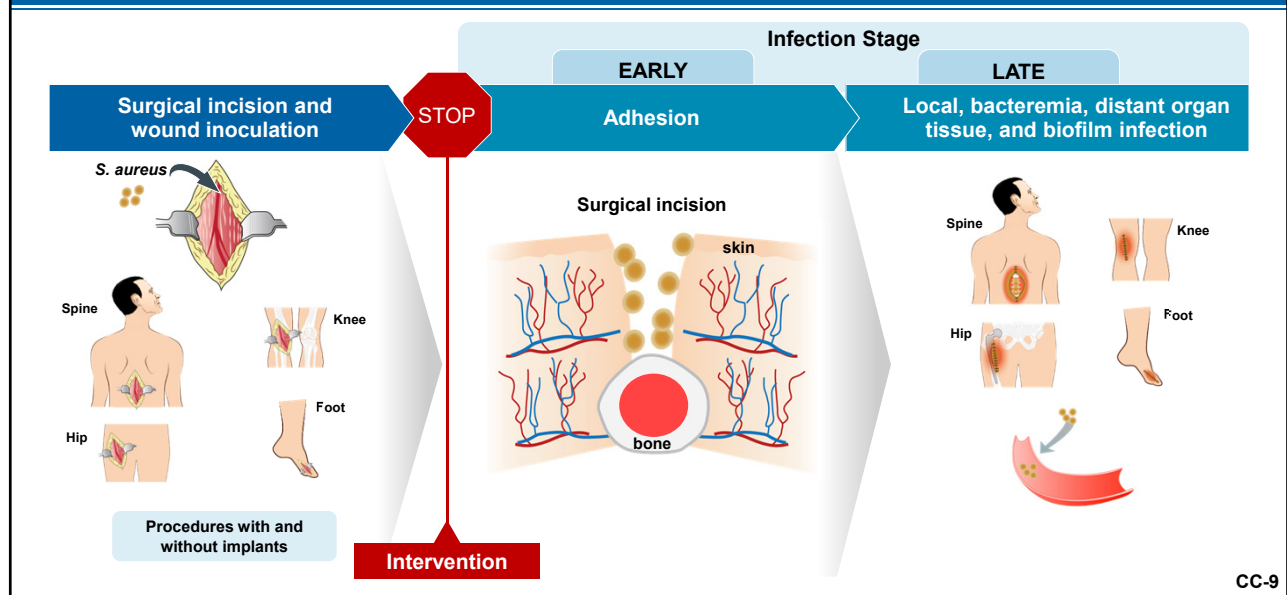
CC-7

Pathophysiology of *S. aureus* Surgical Site Infection is Consistent Across Elective Orthopedic Surgical Populations and Procedures



CC-8

Pathophysiology of *S. aureus* Surgical Site Infection is Consistent Across Elective Orthopedic Surgical Populations and Procedures



Key Factors Supporting SA4Ag Efficacy

- **Targets 3 virulence mechanisms expressed early in infection rather than a single virulence mechanism¹**
- **Antigens have demonstrated efficacy in preclinical models including invasive disease animal models^{2,3,4,5}**
- **Induces functional antibodies against target antigens which:**
 - Facilitate killing of *S. aureus* by opsonophagocytosis²
 - Neutralize virulence pathways directly associated with the target antigens^{4,5}
- **STRIVE population has been chosen as the most stringent population in which to demonstrate vaccine efficacy and safety**
 - Pathophysiology of infection same across orthopedic procedures

1. Anderson et al. *Hum Vaccin Immunother* 2012; 8(11):1585-94; 2. Nanra et al. *Hum Vaccin Immunother* 2013; 9(3):480-7; 3. Fattom et al. *Infect Immun* 1996; 64:1659-65; 4. Scully et al. *Vaccine* 2015; 33(41):5452-7; 5. Anderson et al. *J Infect Dis* 2012; 205(11):1688-96.

SA4Ag Designed to Target Three Key Virulence Factors Expressed Early in Invasive *S. aureus* Infection

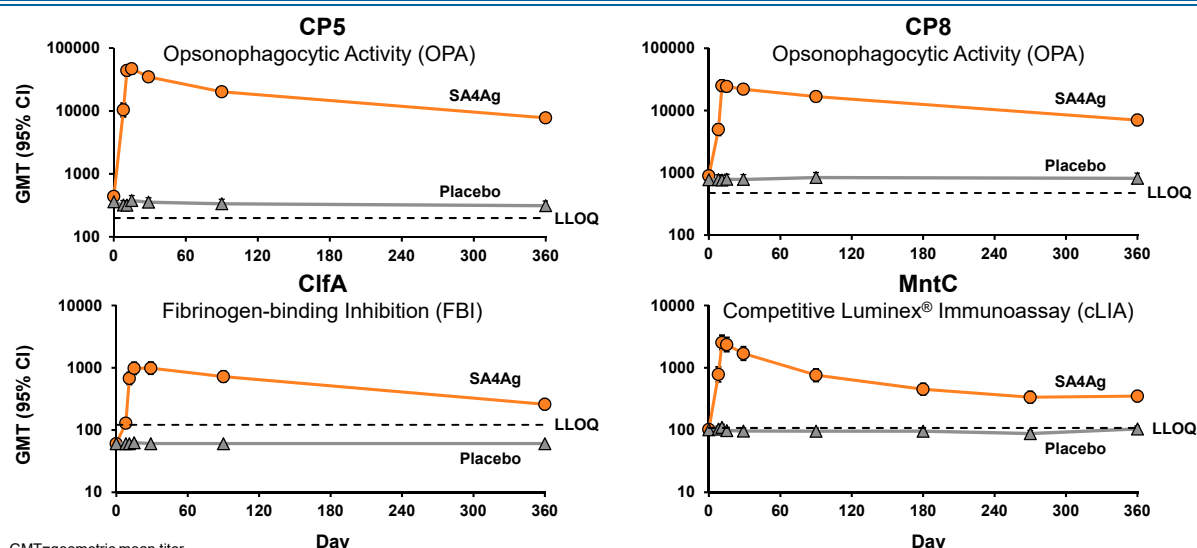
Target Antigens	Virulence Mechanism
Clumping factor A (ClfA): rmClfA	Adhesion to host factors ^{1,2}
Manganese transporter C (MntC): rP305A	Nutrient acquisition ^{3,4}
Capsular polysaccharides (CP5 and CP8): CP5-CRM₁₉₇, CP8-CRM₁₉₇	Immune evasion: Anti-phagocytic ^{5,6}

CP=Capsular Polysaccharide

1. Moreillon et al. *Infect Immun* 1995; 63(12):4738-43; 2. Cheng et al. *FASEB J* 2009; 23(10):3393-404; 3. Anderson et al. *J Infect Dis* 2012; 205(11):1688-96; 4. Handke et al. *PLoS one* 2013; 8(10):e77874; 5. Nanra et al. *Hum Vaccin Immunother* 2013; 9(3):480-7; 6. Thakker et al. *Infect Immun* 1998; 66:5183-9.

CC-11

SA4Ag Demonstrates Functional Immune Response and Safety in Adults 18 to 85 Years



CC-12

SA4Ag Demonstrates Functional Immune Response and Safety in Adults 18 to 85 Years

Opsonophagocytic *S. aureus* Killing Response in 18 to 85 Year Old Subjects (CP5 OPA)

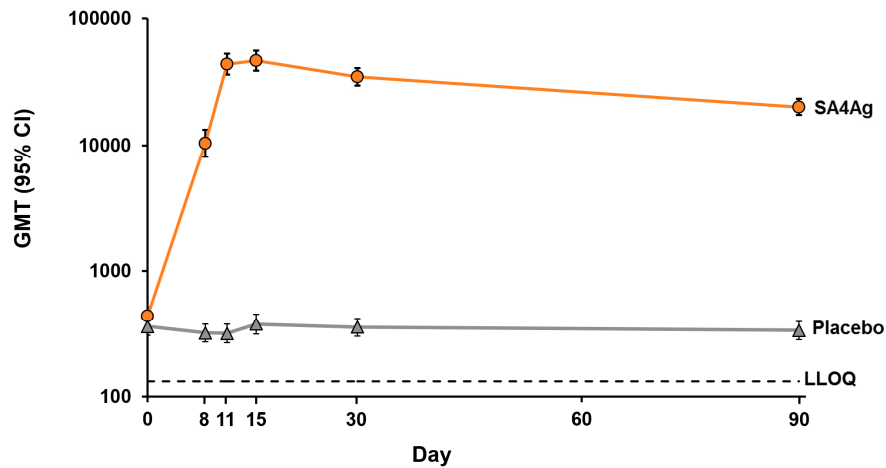


Figure shows combined data for SA4Ag recipients (final dose level) in US adults 18 to 85 years of age (studies B3451001 and B3451011)

STRIVE Study

ST*aphylococcus aureus* su**R**gical Inpatient **V**accine **E**fficacy

- Rationale for selection of elective spinal surgery
- Study design
- Safety assessments

Considerations for Selecting an Elective Orthopedic Efficacy Study Population

- **Competent immune system**
- **Ability to be vaccinated prior to a known period of risk**
- **Predictable incidence of invasive *S. aureus* (ISA) disease**
- **Ability to observe an ISA clinical endpoint within a defined period of risk**

STRIVE satisfies all these criteria and permits an expedient determination of efficacy and safety and is representative of all elective orthopedic surgical populations

CC-15

Challenges of SA4Ag Efficacy Clinical Trials in Elective Orthopedic Surgeries

**Hip arthroplasty
infection rate:
~0.40%^a**

- **~25,000 subjects**
- **Study conduct >10 years**

**Knee arthroplasty
infection rate:
~0.25%^a**

- **~40,000 subjects**
- **Study conduct >15 years**

**Phase 3 STRIVE*
infection rate:
~1.4%^a**

- **~6,000 subjects**
- **Study conduct ~6 years**

*~90% power to demonstrate 95% LCI ≥20%. Assumes true vaccine efficacy ≥70%
a. Pfizer analysis of the US Premier Healthcare Database (2010-2014) – Pfizer Data on File

CC-16

Orthopedic Surgery: Clinical Trial Operational Challenges

• STRIVE experience:

- After 28 months of enrollment: ~1900 subjects randomized from ~100 sites in US, Canada, Japan, and 6 countries in Europe
- >1700 investigators contacted to identify current ~100 study sites
- Key challenges are related to identifying sites with:
 - Adequate volume of elective multilevel instrumented spinal surgery
 - Experience in clinical trials
 - Clinical research infrastructure

CC-17

There is a Large Potential U.S. Public Health Impact of a 70% Efficacious *S. aureus* Vaccine

Estimated Number of *S. aureus* Infection-related Outcomes Prevented through Postoperative Day 90 Following Major Elective Orthopedic Surgeries (2021-2030)

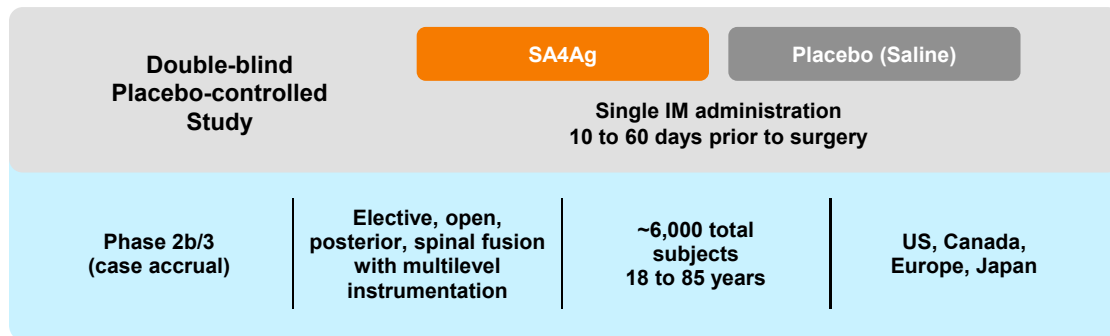
	Arthroplasty	Spinal	Total
Number of surgical procedures^a	17,805,216	9,724,247	27,529,463
Hospitalizations prevented^b	70,168	27,211	97,379
Deaths prevented^b	1,149	1,094	2,243

a. Projected surgical volumes are from Life Science Intelligence Report 2015, with adjustment based upon HCUP (2014) data analysis to eliminate overlapping multiple surgeries and emergent surgeries.

b. Hospitalization and death estimates based on *S. aureus* infection rates (overall and invasive) and case fatality rates come from Pfizer Premier Study. Assume each invasive infection results in one hospitalization on average.

CC-18

Ongoing STRIVE Study



CC-19

STRIVE Primary Outcome

Number of subjects in each treatment group with postoperative *S. aureus* deep incisional or organ/space surgical-site infection and/or bloodstream infection occurring within **90 days of elective multilevel instrumented spinal surgery**

CC-20

STRIVE Protocol Defined Infections (PDI)

- Postoperative infections occurring after surgery caused by *S. aureus* will be prospectively evaluated and independently adjudicated through 180 days post-surgery
- PDI clinical criteria utilizes NHSN^a surveillance criteria to define all endpoints:

Deep incisional, organ/space SSI, bloodstream infections (BSI)

All other invasive *S. aureus*

Superficial SSI

a. Adapted from U.S. CDC's National Health Safety Network Surgical Site Infections, January 2014 Edition

CC-21

STRIVE Includes Rigorous Assessments to Support the Safety of SA4Ag

- Comprehensive safety assessments from day of vaccination through 6 months after the index surgery
- Local reactions and systemic events for 10 days using e-diaries
- Adverse events from informed consent to the Day 42 postoperative evaluation
- All serious adverse events from informed consent to study completion (180 Days postoperative)
- Safety data monitored by external Data Monitoring Committee

CC-22

STRIVE Results Can Be Applied to Other Elective Orthopedic Surgeries

- **Pathogenesis is similar**
- **Patient demographics and risk factors for developing *S. aureus* SSI are similar**
- **Commonalities in procedural risk factors of orthopedic surgical site infections**

CC-23

Common Pathogenesis Across Elective Orthopedic Surgery Types

- ***S. aureus* is most common cause of SSI across elective orthopedic surgery^{1,2}**
- **Patient colonization is primary source of *S. aureus* inoculation for SSI³**
- **Infecting *S. aureus* strains are not specific to surgery-type⁴**
- **Primary risk period for establishing SSI is during procedure⁵**
 - **Basis for perioperative antibiotic prophylaxis effectiveness⁶**
- **Most SSIs occur within 90 days after surgery⁷**

1. Solomkin et al. *Surg Infect* 2017; 18(4):385-93; 2. Segreti et al. *Surg Infect* 2017; 18(4):394-400; 3. Skramm et al. *J Bone Joint Surg Am* 2014; 96(11):882-8; 4. Pfizer data on file; 5. Cheadle. *Surg Infect (Larchmt)* 2006;7 Suppl 1:S7-11; 6. Bratzler DW et al, *Am J Health-Syst Pharm* 2013; 70:195-283; 7. Analyses for Pfizer by the Premier, Inc. (Charlotte, NC) using data from network of US hospitals that captures 5% of all US admissions (Premier Healthcare Database).

CC-24

SA4Ag Induces a Rapid, Robust and Sustained Functional Antibody Response During Period of Risk

Opsonophagocytic *S. aureus* Killing Response in 18 to 85 Year Old Subjects (CP5 OPA)

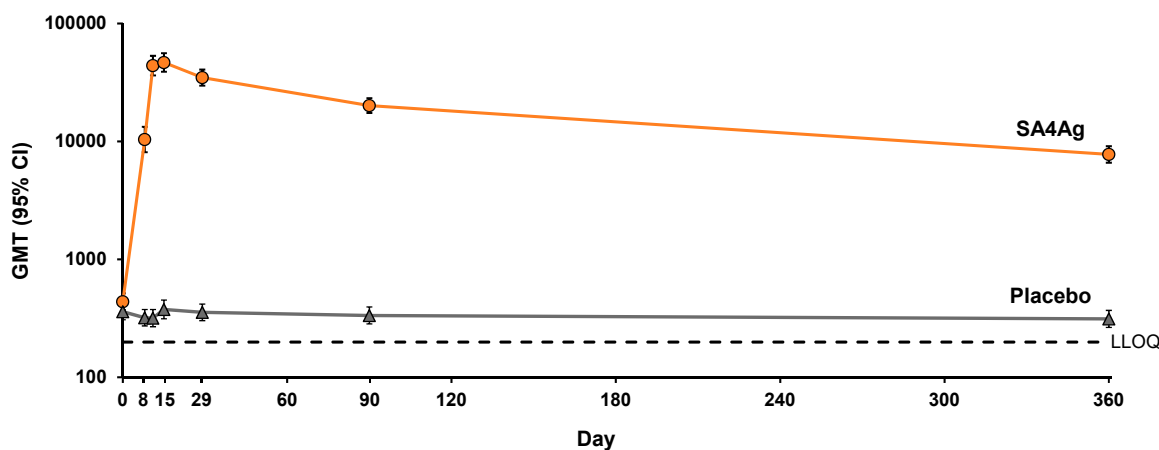


Figure shows combined data for SA4Ag recipients (final dose level) in US adults 18 to 85 years of age (studies B3451001 and B3451011)

CC-25




STRIVE Patient Demographics and Risk Factors for Developing *S. aureus* SSI are Similar Across Orthopedic Surgeries

	Primary Total Knee Arthroplasty N=15,157 ¹ 27,745 ²	Primary Total Hip Arthroplasty N=7,791 ¹ 17,628 ³	Spinal Surgery (+/- implants) N=15,668 ⁴	STRIVE N=1,529 ⁵
Age (mean, years)	67.3	65.4	57.7	61.7
Male (%)	35.5	44.3	50.8	45.2
White (%)	79.3	80.5	83.1	82.2
Diabetes (%)	18.2	11.6	15.4	17.8
Smoking (%)	8.6	13.8	21.9	15.8
COPD (%)	3.7	4.5	3.6	4.3
Congestive heart failure (%)	0.2	0.5	0.2	0.9
Peripheral vascular disease (%)	0.6	0.5	0.8	0.9
BMI (kg/m ²)	32.8	29.8	NA	29.5
American Society of Anesthesiologists (ASA) Score: 3-4 (%)	48.9	43.2	40.8	40.0

1. Pugely AJ et al. *TJA. J Arthroplasty* 2015; 30 (9 suppl):47-50. ACS NSQIP: 2005-2010 – TKA (15,157)/THA (7,791); age, gender, race, diabetes, smoking, COPD, congestive heart failure;
2. Duchman et al. *J Bone Joint Surg Am* 2014; 96 (16):1387-94. NSQIP 2005-2011 – peripheral vascular disease, ASA; 3. Belmont et al. *J Arthroplasty* 2014; 29 (10): 2025-30. ACS NSQIP: 2006-2011- BMI,
ASA, peripheral vascular disease; 4. Pugely et al. *SPINE* 2014; 39 (9): 761-768 (65% with no implant [discectomy/laminectomy] and 35% with implant [spinal fusion/multilevel spinal deformity]).
5. STRIVE Subjects completing index surgical procedure as of 1 October 2017 (open database).

CC-26

Commonalities in Procedural Risk Factors of Orthopedic Surgical Site Infections

	Total Knee Arthroplasty	Total Hip Arthroplasty	Spinal Surgery (+/- implants)	STRIVE
Procedural overview	Dermis → dissects between the muscles, tendons, and nerves to reach the joints/bone			
Implanted material (if used)	Metal alloys (titanium, stainless steel or cobalt-chromium), plastics (polyethylene), ceramic, bone cement, bone graft			
Incision length: Variable 2 to >12 inches				
Mean OR time, (±SD) minutes	96.9 (37.9) ¹	97.6 (42.9) ²	144.2 (94.6) ³	270.0 (122.9) ⁴

OR=operating room

1. Belmont et al. *J Bone Joint Surg Am* 2014; 96(1): 20-6. 2. Belmont et al. *J Arthroplasty* 2014; 29(10): 2025-30.3. Abt et al. *J Clin Neurosci* 2017; 36: 37-42. 4. STRIVE Subjects completing index surgical procedure as of 1 October 2017 (open database).

CC-27

STRIVE Population is Representative of Elective Orthopedic Surgery Patients

Pathogenesis is similar across elective orthopedic surgery types

Patient demographics and risk factors for developing *S. aureus* SSI are similar to STRIVE

Commonalities in procedural risk factors of orthopedic surgical site infections

CC-28

SA4Ag Clinical Development Program to Support an Indication in Elective Orthopedic Surgery

Study Number	Type	Age in years	Final Formulation SA4Ag Vaccinated Subjects		
			Non-surgical	Surgical	Placebo
B3451001	Phase 1/2a: Dose escalation/Safety & Immunogenicity	18-64	112	NA	112
B3451011	Phase 1/2a: Dose escalation/Safety & Immunogenicity	65-85	57	NA	60
B3451014	Phase 2a: Antibody persistence up to 36 months after SA4Ag	18-85	-	NA	-
B3451015	Phase 1: Safety & immunogenicity for final SA4Ag clinical trial material for efficacy study	18-64	100	NA	0
B3451003	Phase 1/2a: Safety & immunogenicity in Japanese subjects	20-85	68	NA	68
B3451002	(STRIVE) Phase 2b→3: Efficacy and safety in subjects scheduled to undergo elective, open posterior, spinal fusion procedures with multilevel instrumentation	18-85	NA	3,000	3,000
B3451006	Phase 3: Clinical lot consistency	18-49	2,061	NA	687
Subjects Totals			2,398	3,000	3,927
<div> <div>completed</div> <div>ongoing</div> <div>planned</div> </div>			5,398		

NA=Not Applicable

Total vaccinated subjects in Phase 1 and Phase 1/2a studies=1,379 subjects (SA3Ag=350 and SA4Ag [all doses]=687, placebo=342)

CC-29

Pfizer Proposal

- **Assume** the STRIVE study demonstrates SA4Ag acceptable safety and efficacy in adults
- **Then** STRIVE results should be representative of safety and efficacy in elective orthopedic surgical populations 18 years of age and older, and should support the following indication:

“Active immunization for the prevention of postoperative invasive disease caused by *Staphylococcus aureus* in adults 18 years of age and older undergoing elective orthopedic surgery”

CC-30